

REMARKS

Reconsideration is respectfully requested in view of the remarks which follow.

The claims presently pending in the application are 1-9, inclusive.

Claims 1-5, 8 and 9 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over an article by Quelet et al. when combined with JP 57009734. This rejection is respectfully traversed.

The Examiner maintains that the Japanese reference is considered to complement the reaction described in Quelet (which does not disclose any oxidations) with the last step of the present process, i.e. "*the oxidation of the benzyl alcohol in the liquid phase to alkoxybenzaldehyde (heliotropine derivative), using Pa±Pt, or Pb±Cu as catalysts*".

This, however, is not the specific oxidation step of the claimed process. The oxidation step in claim 1 (as amended during the PCT International Phase and as entered in the present US National Phase) recites:

*(iii) catalytic oxidation of the alcohol (III) to form the compound (IV) wherein the passage (iii) is conducted by treating in the liquid phase the product of passage (ii) with air or oxygen and an alkaline hydroxide used in a hydroxide/alcohol (III) equivalent ratio between 1 and 2, in the presence of a suitable oxidation catalyst.*

The reference JP5700974 fails to disclose or suggest a specific 1:2 base/alcohol equivalent ratio. On the contrary, the reference explicitly suggests carrying out this reaction in the absence of an alkali compound (cf. the penultimate sentence of the abstract). This teaching would lead one of ordinary skill in the art away from the claimed invention. In fact, JP5700974 does not attach any special significance to the presence of a base, and even considers it as a disturbing factor.

In view of the foregoing, one of ordinary skill in the art when combining the Quelet reference with JP5700974, would be taught by the JP '974 reference to avoid any bases in the oxidation step. However, even if the skilled artisan were to attempt to use a base (going against the teaching of JP '974), he would certainly use quantities which were much lower than equimolar with the alcohol, since the base is considered to be detrimental to success.

The present process as claimed proceeds in exactly the opposite sense by specifying the criticality of large amounts of alkaline hydroxide (from 1 to 2 equivalents with respect to the alcoholic substrate). As supported by the specification (page 7, lines 18-19), the effectiveness of the reaction was surprisingly found to increase as the pH increases, with no reduction of selectivity.

The example at page 9 of the specification demonstrates that the process of the invention works at the highest efficiency with conventional oxidation catalysts (e.g. simple metallic Pt), the conversion rate being substantially 100% (99.6%). Selectivity data are supplied by the enclosed additional report (Annex 1), where a number of oxidations have been performed in accordance with the invention, using an alkaline hydroxide/alcohol(III) equivalent ratio of 1/1, and Pt as oxidation catalyst. The results show selectivity rates in the range of 90-95%, conversion rates in the range of 95-100%, and yield in the range of 89-93%.

It will be appreciated that the remarkable results in Example 9 and the enclosed test (Annex 1) were obtained starting from crude piperonyl alcohol, i.e. containing impurities resulting from steps i) and ii) of the claimed process (cf. page 9, line 13). Thus, the above advantages have been obtained within a real industrial synthetic cycle, in a situation closer to real-life and being more disadvantaged than JP5700974 which operates on pure piperonyl alcohol.

The patentability of the present claims 1-9 *vis à vis* the cited prior art is further confirmed by the enclosed fully positive IPER issued in the PCT International Phase for the present case (Annex 2).

In summary, the claimed, highly effective, industrially easy-to-implement synthesis of heliotropine and its derivatives clearly distinguishes over the combination of art applied by the Examiner. Accordingly, the § 103(a) rejection has been overcome and its withdrawal is solicited.

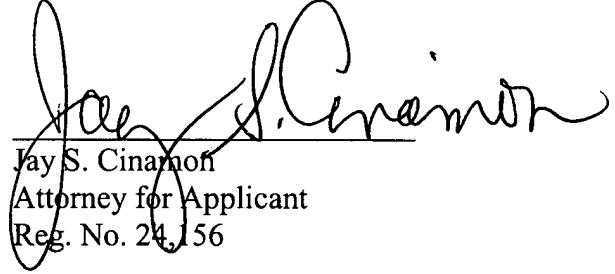
The issuance of a Notice of Allowance is respectfully requested.

Please charge any fees which may be due and which have not been submitted herewith to our Deposit Account No. 01-0035.

Respectfully submitted,

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By

  
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## ANNEX 1

Oxidation of crude piperonyl alcohol to heliothropin was performed in a number of tests, using metallic platinum as a catalyst, and sodium hydroxide in a 1:1 equivalent ratio with respect to pyperonyl alcohol. The results obtained are as follows.

Test no.	Yield heliothropin (%)	Alcohol Conversion (%)	Selectivity (%)
1	92.3	97.9	94.3
2	91.0	100.0	91.0
3	89.4	99.4	89.9
4	93.2	97.9	95.2
5	90.1	98.2	91.7
6	89.7	95.6	93.8
7	89.5	95.0	94.2
8	91.6	98.4	93.1
9	89.0	97.5	91.3

From the  
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To:

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NOTIFICATION OF TRANSMITTAL OF  
THE INTERNATIONAL PRELIMINARY  
REPORT ON PATENTABILITY

(PCT Rule 71.1)

Date of mailing  
(day/month/year)

16.08.2005

Applicant's or agent's file reference  
4540PTWO-ca

IMPORTANT NOTIFICATION

International application No.  
PCT/EP2004/052710

International filing date (day/month/year)  
28.10.2004

Priority date (day/month/year)  
30.10.2003

Applicant  
ENDURA S.P.A. et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary report on patentability and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/B/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary report on patentability. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

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# PCT

## INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

### (PCT Article 36 and Rule 70)

Applicant's or agent's file reference 4540PTWO-ca	<b>FOR FURTHER ACTION</b>	
	See Form PCT/IPEA/416	
International application No. PCT/EP2004/052710	International filing date (day/month/year) 28.10.2004	Priority date (day/month/year) 30.10.2003
International Patent Classification (IPC) or national classification and IPC C07D317/54		
Applicant ENDURA S.P.A. et al.		

<p>1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 5 sheets, including this cover sheet.</p> <p>3. This report is also accompanied by ANNEXES, comprising:</p> <p>a. <input type="checkbox"/> <i>(sent to the applicant and to the International Bureau) a total of sheets, as follows:</i></p> <ul style="list-style-type: none"> <li><input type="checkbox"/> sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).</li> <li><input type="checkbox"/> sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.</li> </ul> <p>b. <input type="checkbox"/> <i>(sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).</i></p>
<p>4. This report contains indications relating to the following items:</p> <ul style="list-style-type: none"> <li><input checked="" type="checkbox"/> Box No. I Basis of the opinion</li> <li><input type="checkbox"/> Box No. II Priority</li> <li><input type="checkbox"/> Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</li> <li><input type="checkbox"/> Box No. IV Lack of unity of invention</li> <li><input checked="" type="checkbox"/> Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</li> <li><input type="checkbox"/> Box No. VI Certain documents cited</li> <li><input type="checkbox"/> Box No. VII Certain defects in the international application</li> <li><input type="checkbox"/> Box No. VIII Certain observations on the international application</li> </ul>

Date of submission of the demand 25.05.2005	Date of completion of this report 16.08.2005
Name and mailing address of the International preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Steendijk, M Telephone No. +49 89 2399-8460



# INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.  
PCT/EP2004/052710

## Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.
  - This report is based on translations from the original language into the following language, which is the language of a translation furnished for the purposes of:
    - international search (under Rules 12.3 and 23.1(b))
    - publication of the international application (under Rule 12.4)
    - international preliminary examination (under Rules 55.2 and/or 55.3)
2. With regard to the **elements\*** of the international application, this report is based on (*replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report*):

### Description, Pages

1-10 as originally filed

### Claims, Numbers

1-9 received on 25.05.2005 with letter of 23.05.2005

- a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3.  The amendments have resulted in the cancellation of:
  - the description, pages
  - the claims, Nos.
  - the drawings, sheets/figs
  - the sequence listing (*specify*):
  - any table(s) related to sequence listing (*specify*):
4.  This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
  - the description, pages
  - the claims, Nos.
  - the drawings, sheets/figs
  - the sequence listing (*specify*):
  - any table(s) related to sequence listing (*specify*):

\* If item 4 applies, some or all of these sheets may be marked "superseded."

**INTERNATIONAL PRELIMINARY REPORT  
ON PATENTABILITY**

International application No.  
PCT/EP2004/052710

**Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

**1. Statement**

Novelty (N) Yes: Claims 1-9

No: Claims

Inventive step (IS) Yes: Claims 1-9

No: Claims

Industrial applicability (IA) Yes: Claims 1-9

No: Claims

**2. Citations and explanations (Rule 70.7):**

**see separate sheet**

**INTERNATIONAL PRELIMINARY  
REPORT ON PATENTABILITY  
(SEPARATE SHEET)**

International application No.

PCT/EP2004/052710

1) The present application relates to the preparation of aldehyde derivatives of alkoxylated benzenes, in particular piperonal, by catalytic conversion of the corresponding alcohols in the liquid phase in the presence of 1-2 equivalents of alkaline hydroxide, which in turn are prepared from the corresponding benzylchlorides via the corresponding benzyl acetates.

The amendments are based on claim 8 in combination with statements on page 7 as originally filed.

2) Cited documents

D1: JP 55 022615 A

D2: JP 57 009734 A

D3: DATABASE CAPLUS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 1937, QUELET ET AL.: "Synthesis of anisic alcohol" XP002322521 retrieved from STN Database accession no. 1937:817

Ref AR

D4: BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, JAPAN PUBLICATIONS TRADING CO. TOKYO, JP, vol. 62, no. 11, November 1989 (1989-11), pages 3567-3571, XP001189402 ISSN: 0009-2673

3) Novelty

Documents D1 and D2 describe the preparation of piperonal by catalytic oxidation of piperonyl alcohol; these documents do not describe the obtention of the alcohol from the chloride as presently defined nor do they specify the use of the defined amounts of alkaline hydroxide.

Documents D3 and D4 describe the preparation of alkoxylated benzyl alcohols or acetates from the corresponding benzyl chlorides. The documents do, however, not specifically describe the catalytic preparation of the benzyl aldehydes from the benzyl alcohols as presently defined.

4) Inventive step

The present application shows in the example on page 9 high conversion of the piperonyl alcohol by use of 1-2 equivalents of alkaline hydroxide, which has been

confirmed to proceed with high selectivity.

In the light of D1 and D2 as closest prior art, which already describe the conversion of relevant benzyl alcohols to benzyl aldehydes, the problem underlying the present application seems to reside in the provision of a convenient, possibly improved process for preparing the benzyl aldehyde.

In this context it is observed, that document D1 describes generally lower conversion/selectivity rates than presently shown and that document D2 describes Pb- or Cu-mixed catalysts preferably used without an alkali compound.

It would not seem obvious to the person skilled in the art that increased conversion/selectivity rates could be obtained by the use of the defined amounts of alkaline hydroxides.

**5) Further observations**

The description, in particular page 7, line 20, requires adaptation to the new claims.

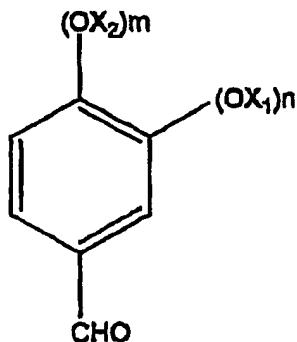
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25. 05. 2005

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## AMENDED CLAIMS

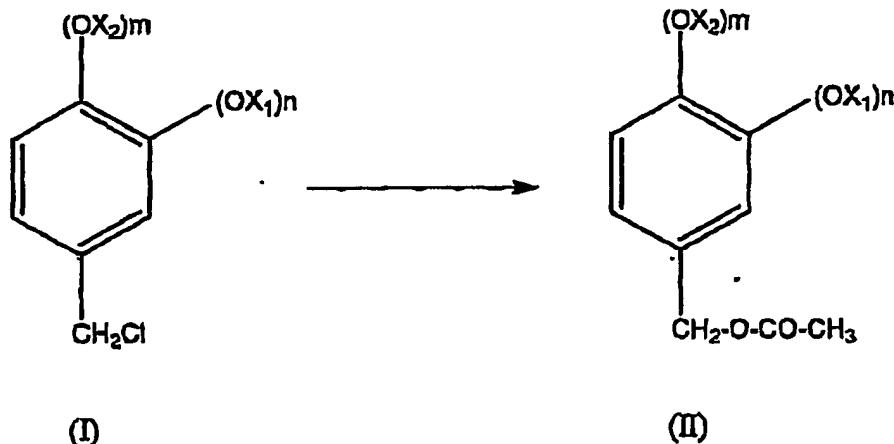
## 1. Process for obtaining a compound of formula (IV)



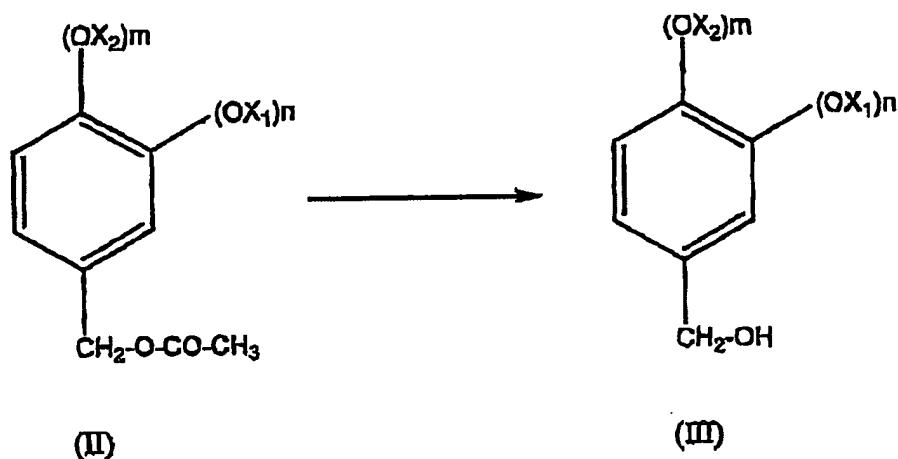
(IV)

5 in which  $X_1$  and  $X_2$ , the same or different, are linear or branched C1-C8 alkyls, n and m are 0,1 or 2, with the proviso that n and m cannot be simultaneously 0; or  $(OX_1)_n$  and  $(OX_2)_m$  taken together form an O-T-O group where T is chosen from - $CH_2$ -, - $CH_2CH_2$ -, - $CH_2CH_2CH_2$ -, - $C(CH_3)_2$ -,  
 said process comprising the following passages:

10 (i) treating a chloromethyl derivative of formula (I) with an alkaline acetate to form the acetyl derivative of formula (II), where  $X_1$ ,  $X_2$ , m and n have the aforesaid meanings;



(ii) hydrolyzing compound (II) to form the alcohol (III), where  $X_1$ ,  $X_2$ ,  $m$  and  $n$  have the aforesaid meanings;



5

(iii) catalytic oxidation of the alcohol (III) to form the compound (IV):

wherein the passage (iii) is conducted by treating in the liquid phase the product of passage (ii) with air or oxygen and an alkaline hydroxide used in a hydroxide/alcohol (III) equivalent ratio between 1 and 2, in the presence of a suitable oxidation catalyst.

10

2. Process as claimed in claim 1, wherein  $X_1$  and  $X_2$  are chosen from a C1-C4 alkyl or taken together correspond to the  $-O-CH_2-O-$  group.

3. Process as claimed in claims 1-2, wherein the passage (i) is conducted by adding an organic solution of the derivative (I) to an aqueous solution containing an alkaline acetate such that, in the resultant mixture, the volume of water constitutes at least 50% of the organic phase.

4. Process as claimed in claim 3, wherein the molar ratios of alkaline acetate to chloromethyl derivative (I) are between 1:1 and 3:1 and the reaction temperature is between 40°C and 85°C.

5. Process as claimed in claim 4, wherein the molar ratios of alkaline acetate to chloromethyl derivative (I) are between 1.3:1 and 1.6:1 and the reaction temperature is between 70°C and 80°C.

6. Process as claimed in claims 1-5, wherein the passage (ii) is conducted by

adding aqueous NaOH and a phase transfer catalyst of the ammonium salts group, to the product of passage (i).

7. Process as claimed in claim 6, wherein the molar ratio of NaOH to chloromethyl derivative (I) is between 3:1 and 1:1 and that of the phase transfer catalyst to NaOH is between 1:100 and 1:400, the reaction being conducted at a temperature between 60°C and 85°C.

5 8. ~~Process as claimed in claims 1-7, wherein the passage (iii) is conducted by treating the product of passage (ii) with air or oxygen and an alkaline hydroxide, in the presence of a suitable oxidation catalyst.~~

10 9. ~~Process as claimed in claim 8, wherein the oxidation catalyst is chosen from Ru, Pd, Pt, Au, said elements being alone or mixed with other metals possibly supported on carbon or aluminium, Raney Ni and Raney Ni heterogenized on hydrotalcite.~~

15 810. Process as claimed in claims 1-79, wherein the passage (iii) is conducted in a water: organic solvent mixture, in which the weight ratio of water to organic solvent present is between 0.5:1 and 2:1.

911. Process as claimed in claims 1-810, wherein in passage (iii) the weight percentage of the catalyst, considered as 50 wt% wetted relative to the alcohol (III) varies from 1% to 15%, the reaction solvent is a toluene/water mixture, the 20 quantity of base is between 1 0.25 and 2 equivalents relative to the alcohol (III), the reaction temperature is between 20°C and 85°C, and the moles of fed oxygen are 3-6 times in excess of the substrate to be oxidized.

## EXPERIMENTAL TEST

Oxidation of crude piperonyl alcohol to heliothropin was performed in a number of tests, using metallic platinum as a catalyst, and sodium hydroxide in a 1:1 equivalent ratio with respect to piperonyl alcohol. The results obtained are as follows.

Test no.	Yield heliothropin (%)	Alcohol Conversion (%)	Selectivity (%)
1	92.3	97.9	94.3
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8	91.6	98.4	93.1
9	89.0	97.5	91.3